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August 7, 2000

Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
United States Food & Drug Administration
Room 1061 (HFA-305)
5630 Fishers Lane
Rockville, MD 20852

Re: Review of criteria used to determine whether specific laboratory tests are waived from certain requirements of the Clinical Laboratory Improvement Amendments of 1988 (CLIA): General and Specific Questions for Public Input

Ladies & Gentlemen,

Beckman Coulter appreciates the opportunity to respond to the FDA's questions for the public workshop on CLIA waiver criteria on August 14th and 15th, 2000. This letter provides summary comments regarding our responses. The specific questions and our responses are provided in the attached table.

Beckman Coulter is a major international manufacturer and worldwide distributor of medical and scientific test systems, including *in vitro diagnostic* test systems. The company was formed in October 1997 by the combination of what was then Beckman Instruments, Inc., based in Fullerton, California and Coulter Corporation, based in Miami, Florida. Beckman Coulter headquarters are located in Fullerton, California, with manufacturing facilities located in Fullerton, Brea, Carlsbad, and Palo Alto, California; Miami, Florida; Florence, Kentucky; Chaska, Minnesota; and Galway, Ireland. The company's 1999 sales totaled \$1.8 billion.

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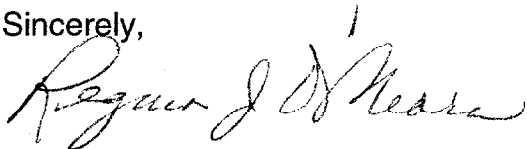
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We support the effort by DCLD to standardize and document the criteria by which *in vitro diagnostic* tests may be classified within or waived from certain aspects of CLIA. We are also pleased to see this effort within the first year of FDA assuming complexity rating from the National Centers for Disease Control (CDC). From our perspective, the goal is to avoid unnecessary overlap between the safety and effectiveness reviews required under Section 510(k) of the FDCA and those criteria that are truly pertinent to a waiver of certain CLIA requirements. The focus for granting of CLIA "waivered" status must continue to be on unreasonable risk of harm to health and not on specific performance characteristics used to determine substantial equivalence or safety of use.

Again, Beckman Coulter appreciates the opportunity to comment on this proposed guidance. Any questions regarding the comments provided in this letter or the attached table can be addressed to my attention at the letterhead address noted below.

Sincerely,

A handwritten signature in cursive script, appearing to read "Regina J. O'Meara".

Regina J. O'Meara
Manager
Legislative Initiatives and Quality Assessments

Attachment: Table of Responses

Specific Responses to General and Specific Questions for Public Input
On Review of criteria used to determine whether
specific laboratory tests are waived from certain requirements of the
Clinical Laboratory Improvement Amendments of 1988 (CLIA)
DCLD Public Workshop, August 14-15, 2000

SECTION	QUESTION	RESPONSE
General Questions for Public Input #1	What criteria should be used to demonstrate that a waived test is a simple laboratory examination and procedure with "an insignificant risk of an erroneous result?"	<ul style="list-style-type: none"> • Demonstration of insignificant risk of an erroneous result can be achieved through studies comparing "CLIA-regulated" lab results to "waived testing" lab results. Participants used in these studies should represent those found in these two settings. It should NOT be expected that a person with no training or prior experience in a medical setting be able to perform waived tests without error. However, error messages built into the device will minimize the risk of reporting out incorrect test results. For example, if a device notifies the user that an "invalid" result has been obtained, the labeling should indicate to the user to repeat the test, or contact the manufacturer for additional assistance. • The statistical numbers used in such studies should be an analysis based upon number of participants, not number of tests performed. The studies seek to demonstrate that multiple users can perform such tests accurately and repeatedly. • Analysis of data collected from such studies should be presented as the correlation of correct results obtained and reported by each user, excluding the number of error messages obtained. Correlation of test result accuracy should demonstrate no "statistically significant" differences between users. • The focus of studies to demonstrate the simplicity of the test should be on the procedure and interpretation of test results labeling. • The "reasonable risk of harm to the patient if a test is not performed correctly" should continue to be a criteria

SECTION	QUESTION	RESPONSE
		<p>used. For example, an HIV test has extremely high standards for sensitivity. If a manufacturer were to demonstrate that their HIV test was 99.9% sensitive, but during user studies using 20 participants, one user gave an erroneous result of false negative, this could be viewed as causing a reasonable risk of harm to the patient.</p> <ul style="list-style-type: none"> • One alternate method for making a determination for waived categorization is by performing studies comparing an already waived test for the same marker to the new test, in the same "waived testing" lab environment. Again, results of these studies would determine there to be no statistically significant difference between the two tests.
General Questions for Public Input #2	What criteria should FDA use to determine if a methodology is "so simple and accurate to render the likelihood of erroneous results by the user negligible?"	<ul style="list-style-type: none"> • Test results should be clear and unambiguous, i.e., "positive", "negative" or a clearly stated quantitative result with appropriate interpretation indicated. • Devices should have built-in mechanisms for notifying the user that the test result is not valid.

SECTION	QUESTION	RESPONSE
General Questions for Public Input #3	What criteria should FDA use in determining that a test will "pose no unreasonable risk of harm to the patient if performed incorrectly?"	<ul style="list-style-type: none"> • Most products under consideration for waived status are for diagnostic markers to be used in conjunction with other appropriate clinical information. Therefore, the result obtained with such a test should not have direct harm to the patient, if such results are reviewed along with other medical information. • The risk of an incorrect result obtained with such assays is also part of the clinical accuracy picture, as stated in questions #1 and #2 above. • Devices having built-in mechanisms for notifying the user that the test result is not valid will significantly minimize the likelihood of an erroneous result from an assay performed incorrectly.
General Questions for Public Input #4	Should the waiver process be different for screening tests that require a second test for confirmation? Since there are no CLIA standards for performance of waived testing, except instructions to follow the manufacturer's package insert, what is the assurance that confirmatory testing will be performed? Should the need for confirmatory testing raise, lower, or have no impact on the threshold for a waiver decision?	<ul style="list-style-type: none"> • The assurance that confirmatory testing is performed is not the responsibility of the waived test manufacturer. It is the responsibility of the medical staff managing patient care. Therefore, the need for confirmation testing should have no impact on the waived test determination.

SECTION	QUESTION	RESPONSE
Specific Questions for Public Input #5	Should the accuracy be determined using comparison of the waiver test to a well-characterized reference method and/or materials, to a designated comparative method and/or materials, to a working laboratory method and/or materials, to a clinical algorithm for diagnosis, and/or to other endpoints?	<ul style="list-style-type: none"> • For studies to determine waived status, comparing results obtained from "CLIA-regulated" personnel vs. "waived facility" personnel can be performed using well-characterized reference materials. The key to these studies are performing the procedure and interpreting the test results properly, and comparing <i>agreement</i> between test methods or personnel. The 510(k) clinical and analytical studies are what is used to demonstrate <i>accuracy</i> • This may also be obtained by comparing the results of one waived test to another, in the same clinical setting. • Clinical accuracy algorithms and diagnostic endpoints are not relevant to assessing the ability of persons to perform the test.

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Specific Questions for Public Input #6	How many samples, what types of samples (real or artificial) by how many users and how many sites are appropriate to evaluate accuracy? (Current guidelines being followed by FDA are for performance to be demonstrated by laboratory users at a minimum of one site.)	<ul style="list-style-type: none"> • Studies should be adequate to provide a statistically defensible dataset. Sample collection methods should be separated from the test procedure and interpretation itself. The precedent has already been set for separating sample collection methods, for example, with CLO (Campylobacter-like organisms) tests to determine H. pylori status. These tests require trained personnel to collect the biopsy sample, but the CLO test itself is waived. • Use of real or artificial samples should be allowed to demonstrate that the procedures could be performed accurately. • The number of clinical sites is not relevant to demonstrating that a test can be waived. It is the number of users, not the number of sites or the location of the sites that is relevant. • When using easily-obtained real or artificial samples, an n=20 is statistically defensible. However, flexibility should be considered when real samples might be difficult to obtain for a particular marker.
Specific Questions for Public Input #7	What should be the background of these users?	<ul style="list-style-type: none"> • Studies comparing "CLIA-regulated" vs. "waived testing" labs should use employees representative of those performing such tests. • Studies comparing one waived test to another should use employees representative of waived testing labs (e.g., POLs).

SECTION	QUESTION	RESPONSE
Specific Questions for Public Input #8	What performance criteria (statistical or clinical) should FDA apply to the accuracy threshold for a waived test (e.g., t- test or McNemar test at key decision points, description of performance with confidence intervals at key decision points, use of set performance standards using a receiver operator curve – 80%, 90%, 95%, or other – at key decision points, and/or others)?	<ul style="list-style-type: none"> Performance criteria should be statistical not clinical. The evaluations being performed for determination of waived testing are based on performing the procedure and interpreting the test results, not the clinical accuracy of the marker.
Specific Questions for Public Input #9	How should FDA define precision for purposes of waiver determination, what types of samples, how many and what types of operators/sites are appropriate? Current CDC recommendation is for 20 samples at three levels representing appropriate decision points to be tested at three sites by lay users using materials in either artificial and/or real matrices depending on availability and biohazard issues.	<ul style="list-style-type: none"> Precision for purposes of waiver determination is not relevant. As part of the 510(k) requirements, demonstration of analytical accuracy and reproducibility are already reported in the filing. The evaluations being performed for determination of waived testing are based on performing the procedure and interpreting the test results, not the precision of the test. Again, the number of sites is not relevant, the number of users is.
Specific Questions for Public Input #10	What performance thresholds should FDA use to determine whether the precision studies are appropriate for waiver status (e.g., ANOVA analysis, use of a predefined performance goals such as Tonk's formula, or percent agreement out of total repeat runs)?	<ul style="list-style-type: none"> Assay precision studies are not relevant.

SECTION	QUESTION	RESPONSE
Specific Questions for Public Input #11	What interference studies are appropriate to establish performance of waived tests?	<ul style="list-style-type: none"> This question is not specific to waived tests. All tests under evaluation of a 510(k) require interference studies. These studies evaluate the specificity of the marker used in the test, not whether the test is complex or simple to perform and interpret. No specific interference studies for waived tests should be designated.
Specific Questions for Public Input #12	What environmental studies or flex (stress) studies are appropriate to establish performance of waived tests?	<ul style="list-style-type: none"> This question is not specific to waived tests. All tests under evaluation of a 510(k) require environmental (stability) studies. These studies evaluate the stability of the marker used in the test, not whether the test is complex or simple to perform and interpret. No specific environmental studies for waived tests should be designated.
Specific Questions for Public Input #13	What additional studies (if any) should be submitted for evaluation of qualitative tests for waiver?	<ul style="list-style-type: none"> Only studies evaluating the user's ability to perform the procedure and interpret test results should be required. Built-in mechanisms for notifying the user that the test result is not valid should be demonstrated by the manufacturer.
Specific Questions for Public Input #14	What additional studies (if any) should be submitted for evaluation of quantitative tests for waiver?	<ul style="list-style-type: none"> Only studies evaluating the users ability to perform the procedure and interpret test results should be required. Built-in mechanisms for notifying the user that the test result is not valid should be demonstrated by the manufacturer.

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